(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 March 2002 (07.03.2002)

PCT

(10) International Publication Number
WO 02/17905 A2

(51) International Patent Classification[7]: A61K 31/195

(21) International Application Number: PCT/EP01/10041

(22) International Filing Date: 30 August 2001 (30.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00118968.7 1 September 2000 (01.09.2000) EP

(71) Applicant *(for all designated States except US)*: **NOVARTIS CONSUMER HEALTH S.A.** [CH/CH]; Route de L'Etraz, CH-1260 Nyon (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **SALLIN, Dominique** [CH/CH]; Ch. de la Chavane 14, CH-1196 Gland (CH). **KIENZLER, Jean-luc** [FR/FR]; Resid. Prenepla 29, F-01210 Ornex (FR). **SCHUMANN, Phyllis** [US/CH]; Place de Savoie 2, CH-1260 Nyon (CH). **ANCEREWICZ, Jacek** [CH/CH]; Ch. Emile Kueffer 10, CH-1110 Morges (CH).

(74) Agent: **BECKER, Konrad**; Novartis AG, Patent & Trademark Department, CH-4002 Basel (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/17905 A2

(54) Title: TREATMENT OF BURNS

(57) Abstract: The invention relates to the topical use of diclofenac, and topically acceptable salts thereof, (for the manufacture of a topical medicament) for the topical treatment of burns.

Treatment of Burns

The invention relates to the topical (= external) treatment of burns including sunburn with diclofenac or a topically acceptable salt thereof.

The topical application of diclofenac, or topically acceptable salts thereof, for the treatment of e.g. back pain, muscle pain, sprains, bruises, lumbago, epicondylitis, osteoarthritis or rheumatic arthritis is known in the art.

It has now surprisingly been found that by topical application of diclofenac, or a topically acceptable salt thereof, burns of the skin including sunburns can be treated very effectively, which inter alia means that the healing process is promoted dramatically and that the distress of a patient suffering from a burn is alleviated rapidly.

Therefore, the invention relates to the use of diclofenac, or a topically acceptable salt thereof, (for the manufacture of a topical medicament) for the topical treatment of burns including sunburn.

Burns can be caused e.g. by radiation, e.g. sunburn, or e.g. by contact with hot solid objects, such as a hot plate, hot liquids, such as hot water, or hot gases.

Diclofenac is 2-(2,6-dichloroanilino)-phenylacetic acid (= diclofenac free acid). Topically applicable salts of diclofenac are e.g. diclofenac sodium, diclofenac potassium, diclofenac diethylammonium and diclofenac epolamine, with diclofenac diethylammonium, diclofenac epolamine and diclofenac sodium being preferred. Especially preferred are diclofenac diethylammonium and diclofenac sodium - in one particular embodiment diclofenac diethylammonium, and in another particular embodiment diclofenac sodium.

Diclofenac can be applied - typically in the form of a topical pharmaceutical composition - to any portion of the skin.

The beneficial properties of diclofenac when topically administered in the treatment of burns including sunburn can be demonstrated, for example, in the following tests.

(1) In 60 guinea pigs erythema of sunburn are induced by UV radiation [with different irradiation doses of 1, 5 and 10 MED (1 MED = minimal erythemal dose, i.e. the irradiation dose which is just sufficient to induce erythema)]. A topical formulation comprising 1.16% diclofenac diethylammonium [corresponding to 1% diclofenac sodium] (Voltaren® Emulgel®) is applied on the irradiated skin (either 2 mg/cm^2, 10 mg/cm^2 or 50 mg/cm^2). The erythema is strongly reduced in a dose-related manner and significantly better than with placebo.

(2) In an analogous manner as described in (1), a topical test formulation comprising 1% diclofenac sodium is applied on the irradiated skin (either 2 mg/cm^2, 10 mg/cm^2 or 50 mg/cm^2). The erythema is strongly reduced in a dose-related manner and significantly better than with placebo.

(3) In an analogous manner as described in (1), a topical test formulation comprising 0.29% diclofenac diethylammonium [corresponding to 0.25% diclofenac sodium] is applied on the irradiated skin (either 2 mg/cm^2, 10 mg/cm^2 or 50 mg/cm^2). The erythema is strongly reduced in a dose-related manner and significantly better than with placebo.

(4) In an analogous manner as described in (1), a topical test formulation comprising 0.58% diclofenac diethylammonium [corresponding to 0.5% diclofenac sodium] is applied on the irradiated skin (either 2 mg/cm^2, 10 mg/cm^2 or 50 mg/cm^2). The erythema is strongly reduced in a dose-related manner and significantly better than with placebo.

(5) Several cohorts of 25 hairless rats each are irradiated with UV radiation, and erythema of sunburn are induced in all rats. All rats are then treated with a topical formulation comprising 1.16% diclofenac diethylammonium (Voltaren® Emulgel®) but with the beginning of treatment being different in each cohort. It can be shown that the earlier treatment is started after UV radiation, the more quickly is the reversal of erythema.

(6) Hairless rats with erythema induced by UV radiation are treated with Voltaren® Emulgel® as described under (5). A control group of hairless rats with no erythema is likewise treated with Voltaren® Emulgel®. The total plasma concentration of diclofenac is

determined in both groups. It can be shown that the concentration of diclofenac is essentially the same in both groups. So there is observed no increase of the systemic absorption of diclofenac, if diclofenac is applied to irradiated skin (as compared to non-irradiated skin).

The safety of the compositions of the invention is warranted inter alia by the long-time, proven use of topical diclofenac compositions in other indications, such as back and muscle pain, e.g. via the marketed product Voltaren®Emulgel® and many other topical formulations comprising either diclofenac sodium, diethylammonium or epolamine being on the markets.

In particular, the invention relates to the use of diclofenac, or a topically acceptable salt thereof, where the diclofenac component is present in an amount of from 0.01 up to 15% - preferably of from 0.1 up to 5%, especially of from 0.3 up to 3%, more especially of from 0.4 up to 2.5%, and first and foremost of from 0.5 up to 2% - of the total of the topical composition. A particular embodiment of the invention is characterized by the use of the diclofenac component - in particular diclofenac diethylammonium and diclofenac sodium, especially diclofenac sodium - in an amount of from 0.01 up to 2%, or of from 0.05 up to 1.3%, or of from 0.1 up to 2%, preferably of from 0.1 up to 1%, more preferably of from 0.1 up to 0.7% and most preferably of from 0.1 up to 0.5%, of the total composition. All percentages given are weight-% (w/w), if not indicated otherwise.

Preferably, said topical compositions comprise the diclofenac component in therapeutically effective amounts.

The dosage of the active ingredient may depend on various factors, such as sex, age and individual condition of the patient, as well as on the kind of burn involved. Typically, the topical pharmaceutical compositions - e.g. in the form of an emulsion-gel, gel, cream or ointment - are applied once, twice, three times or four times daily. What is important is that the treatment is started as early as possible after the burn has occurred. Typically, after a first application of topical diclofenac, one can wait for e.g. 3-4 hours before repeating the application. Transdermal patches and bandages comprising a diclofenac component also come into consideration as topical formulations. Those may be applied, for example, once per 16 hours, once daily or once per two or three days, with once per 16 hours or once daily being preferred.

Moreover, the invention relates to a method of treating burns including sunburn which comprises topically administering to a mammal in need of such treatment a therapeutically effective amount of diclofenac or a topically applicable salt thereof.

Pharmaceutical compositions suitable for topical administration are e.g. creams, lotions, ointments, microemulsions, fatty ointments, gels, emulsion-gels, pastes, foams, tinctures, solutions; transdermal therapeutic systems (TTS), in particular transdermal patches; plasters and bandages. Preferred are emulsion-gels, gels, creams, lotions, solutions, transdermal patches, plasters and bandages. In particular preferred are emulsion-gels, gels and transdermal patches, especially emulsion-gels and transdermal patches, and first and foremost emulsion-gels. Said compositions are all known in the art; for further details refererence is made e.g. to US patent 4,551,475, columns 7-9 and US patent 4,917,886, columns 10-12.

For example, emulsion-gels represent topical compositions which combine the properties of a gel with those of an oil-in-water emulsion. In contrast to gels, they contain a lipid phase which due to its fat-restoring properties enables the formulation to be massaged in whilst, at the same time, the direct absorption into the skin is experienced as a pleasant property. In contrast to gels which typically are clear and transparent, emulsion-gels are characterized by a turbid, opaque appearance.

For example, transdermal therapeutic systems (TTS's) contain the diclofenac component typically together with a carrier. Useful carriers may include absorbable, pharmacologically suitable solvents to assist passage of the active ingredient through the skin. The TTS's are, for example, in the form of a transdermal patch comprising (a) a substrate (= backing layer or film), (b) a matrix containing the diclofenac component, optionally carriers and optionally a special adhesive for attaching the system to the skin, and normally (c) a protection foil (= release liner). The matrix (b) is e.g. present as a mono-layer but may also consist of different layers.

The manufacture of the topical pharmaceutical preparations in general is known in the art. Likewise, examples of topical pharmaceutical compositions comprising diclofenac components are known in the art, see e.g. US patent 4,917,886, example 1 (and examples

2-7 as well), or US patent 4,551,475, examples 8-16, or EP 372 527 A1 (e.g. examples 1-6), or EP 621 263 A2 (e.g. examples 1-3).

Example 1: 60 guinea pigs are irradiated by UV light (UV-B) with an irradiation dose of 10 MED (1 MED here corresponds to a radiant exposure of about 78 mJ/cm^2 during 1 min) to induce erythema. The irradiated area has a diameter of ca. 9 mm. After irradiation, the irradiated skin is treated with either Voltaren® Emulgel® (three different strengths: 2 mg, 10 mg or 50 mg diclofenac diethylammonium per cm^2) or placebo. One hour after treatment the irradiated portions of the skin of the animals are inspected. The result is that all three dosages of Voltaren® Emulgel® are statistically significantly more potent than placebo ($p<0.05$) in reducing the erythema induced by 10 MED irradiation.

Example 2: A double-blind controlled clinical study is performed in 24 patients. After evaluation of individual MED's, each patient is irradiated by UV light (UV-B) to induce sunburn, with two different sites being irradiated in each case. The irradiated skin is treated with either Voltaren® Emulgel® or placebo. 1 and 2 hours after treatment, a statistically significant relief of UV induced pain (spontaneous and provoked pain) and erythema (visual score and chromatography) is observed in the patients treated with Voltaren® Emulgel®.

Example 3: A double-blind controlled clinical study is performed in 30 patients. After evaluation of individual MED's, each patient is irradiated by UV light (UV-B) to induce sunburn, with four different sites being irradiated in each case. The irradiated skin is treated with either a topical test formulation comprising 1% diclofenac sodium or placebo. What is measured is the time needed for recovery of the irradiated skin. Said time is statistically significantly shorter in the group treated with diclofenac sodium than in the placebo group. In contrast to the group treated with diclofenac sodium, at first a worsening of skin lesions including development of visible eodema and enlargement of erythema is observed in the placebo group.

Claims

1. Use of diclofenac, or a topically acceptable salt thereof, (for the manufacture of a topical medicament) for the topical treatment of burns including sunburn.

2. Use according to claim 1, where diclofenac, diclofenac sodium, diclofenac potassium, diclofenac diethylammonium or diclofenac epolamine is used.

3. Use according to claim 1, where diclofenac sodium is used.

4. Use according to any one of claims 1 to 3, where the diclofenac component is present in an amount of from 0.01 up to 15 weight-% of the total of the topical medicament.

5. Use according to any one of claims 1 to 3, where the diclofenac component is present in an amount of from 0.1 up to 2 weight-% of the total of the topical medicament.

6. Use according to any one of claims 1 to 3, where the diclofenac component is present in an amount of from 0.5 up to 2 weight-% of the total of the topical medicament.

7. Use according to any one of claims 1 to 3, where the diclofenac component is present in an amount of from 0.1 up to 0.7 weight-% of the total of the topical medicament.

8. Use according to any one of claims 1 to 7, where diclofenac, or a topically acceptable salt thereof, is applied in the form of an emulsion-gel, a gel, a cream, a lotion, a solution, a transdermal patch, a plaster or a bandage.

9. Use according to any one of claims 1 to 7, where diclofenac, or a topically acceptable salt thereof, is applied in the form of an emulsion-gel or a transdermal patch.

10. Use according to any one of claims 1 to 7, where the topical medicament manufactured is in the form of an emulsion-gel, a gel, a cream, a lotion, a solution, a transdermal patch, a plaster or a bandage.

11. Use according to any one of claims 1 to 7, where the topical medicament manufactured is in the form of an emulsion-gel or a transdermal patch.

12. A method of treating burns including sunburn which comprises topically administering to a mammal in need of such treatment a therapeutically effective amount of diclofenac or a topically applicable salt thereof.

13. A method according to claim 12 wherein an emulsion-gel or a transdermal patch is administered topically.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 March 2002 (07.03.2002)

PCT

(10) International Publication Number
WO 02/17905 A3

(51) International Patent Classification[7]: A61K 31/195, A61P 17/02

(21) International Application Number: PCT/EP01/10041

(22) International Filing Date: 30 August 2001 (30.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00118968.7 1 September 2000 (01.09.2000) EP

(71) Applicant *(for all designated States except US)*: NOVARTIS CONSUMER HEALTH S.A. [CH/CH]; Route de L'Etraz, CH-1260 Nyon (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SALLIN, Dominique [CH/CH]; Ch. de la Chavane 14, CH-1196 Gland (CH). KIENZLER, Jean-luc [FR/FR]; Resid. Prencpla 29, F-01210 Ormex (FR). SCHUMANN, Phyllis [US/CH]; Place de Savoie 2, CH-1260 Nyon (CH). ANCEREWICZ, Jacek [CH/CH]; Ch. Emile Kueffer 10, CH-1110 Morges (CH).

(74) Agent: BECKER, Konrad; Novartis AG, Patent & Trademark Department, CH-4002 Basel (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
16 May 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/17905 A3

(54) Title: TREATMENT OF BURNS

(57) Abstract: The invention relates to the topical use of diclofenac, and topically acceptable salts thereof, (for the manufacture of a topical medicament) for the topical treatment of burns.

INTERNATIONAL SEARCH REPORT

Inter[redacted] Application No
PCT/[redacted]01/10041

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61P17/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
PAJ, EPO-Internal, WPI Data, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 17978 A (PITMY INT NV ;MEYER PETRUS JOHANNES (ZA)) 22 May 1997 (1997-05-22) page 22; example 5 page 30, line 20 -page 31, line 9 page 21; example 3	1-6,8,10
Y	---	9,11
X	PATENT ABSTRACTS OF JAPAN vol. 009, no. 021 (C-263), 29 January 1985 (1985-01-29) & JP 59 170011 A (POLA KASEI KOGYO KK), 26 September 1984 (1984-09-26) abstract	1,4-8,10
Y	---	9,11
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 February 2002	01/03/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax (+31–70) 340–3016	Brunnauer, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter[illegible]nal Application No
PCT[illegible]01/10041

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 923 937 A (COUNCIL SCIENT IND RES) 23 June 1999 (1999-06-23) page 8; example 6 page 15, line 29; claim 1	1-6,8,10
Y		9,11
X	US 5 674 912 A (MARTIN ALAIN) 7 October 1997 (1997-10-07) claims 1,4,19 column 50, line 61 - line 65 column 21, line 12 - line 15	1-8,10
Y		9,11
Y	PETERS, P. ET AL: "The effect of topically applied agents on ultraviolet erythema in guinea pigs" AGENTS ACTIONS (1977), 7(5-6), 545-53, XP000995255 abstract page 545 -page 546	1-11
Y	JONSSON C E ET AL: "Impairment of renal function after treatment of a burn patient with diclofenac, a non-steroidal antiinflammatory drug." BURNS, (1995 SEP) 21 (6) 471-3., XP000995264 page 471	1-11
Y	WO 99 16434 A (PARK CHUL MIN ;SAM YANG CO (KR); SONG JIN DEOG (KR); CHOI YOUNG KW) 8 April 1999 (1999-04-08) page 13-16; tables 1-6 claim 1	9,11
Y	EP 0 950 408 A (TEIKOKU SEIYAKU KK) 20 October 1999 (1999-10-20) page 4-5; tables 1-4 claim 1	9,11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/01/10041

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9717978 A	22-05-1997	AU 730495 B2	08-03-2001
		AU 7637196 A	05-06-1997
		BR 9611523 A	28-12-1999
		CA 2237306 A1	22-05-1997
		EP 0866713 A1	30-09-1998
		WO 9717978 A1	22-05-1997
		JP 2000500449 T	18-01-2000
		NO 982161 A	02-07-1998
		NZ 322588 A	28-01-1999
		US 6221377 B1	24-04-2001
		ZA 9609474 A	02-06-1997
JP 59170011 A	26-09-1984	NONE	
EP 0923937 A	23-06-1999	EP 0923937 A2	23-06-1999
US 5674912 A	07-10-1997	AU 690366 B2	23-04-1998
		AU 3859695 A	26-06-1996
		EP 0796107 A1	24-09-1997
		NZ 295303 A	29-07-1999
		WO 9617624 A1	13-06-1996
		ZA 9510376 A	06-10-1997
		US 5981606 A	09-11-1999
		US 5874479 A	23-02-1999
		US 5856364 A	05-01-1999
		US 5641814 A	24-06-1997
		US 5658956 A	19-08-1997
		US 5663208 A	02-09-1997
		US 5648380 A	15-07-1997
		US 5863938 A	26-01-1999
		US 5602183 A	11-02-1997
		US 5614561 A	25-03-1997
		US 5658957 A	19-08-1997
		US 5646190 A	08-07-1997
		US 5692302 A	02-12-1997
		AT 150966 T	15-04-1997
		AU 668084 B2	26-04-1996
		AU 1271892 A	06-10-1992
		CA 2104461 A1	02-09-1992
		DE 69218762 D1	07-05-1997
		DE 69218762 T2	06-11-1997
		EP 0573465 A1	15-12-1993
		JP 6506917 T	04-08-1994
		MX 9200894 A1	01-09-1992
		WO 9215292 A1	17-09-1992
		US 5652274 A	29-07-1997
		US 5633285 A	27-05-1997
		ZA 9201538 A	25-11-1992
WO 9916434 A	08-04-1999	AU 726448 B2	09-11-2000
		AU 9464798 A	23-04-1999
		BR 9815378 A	21-11-2000
		CN 1271280 T	25-10-2000
		EP 1030660 A1	30-08-2000
		JP 2001517696 T	09-10-2001
		WO 9916434 A1	08-04-1999
EP 0950408 A	20-10-1999	JP 11035458 A	09-02-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter[illegible]nal Application No
PCT/[illegible]1/10041

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0950408 A		AU 708584 B2	05-08-1999
		AU 8129598 A	10-02-1999
		DE 69801893 D1	08-11-2001
		DK 950408 T3	28-01-2002
		EP 0950408 A1	20-10-1999
		US 6262121 B1	17-07-2001
		WO 9903461 A1	28-01-1999